DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Mr. Robert B. Clark
Director/Team Leader
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Re: Docket Nos. 99P-1172/CP1 and 98N-0056

Dear Mr. Clark:

On June 9, 1999, the Food and Drug Administration (FDA) issued a Public Health Advisory on liver toxicity associated with the antibiotic Trovan (alatrofloxacin/trovafloxacin). We enclose a copy of the advisory. In light of this advisory and the potential risks associated with Trovan's use, FDA has reconsidered its June 17, 1999 response to your April 23, 1999, citizen petition. At this time, FDA is removing alatrofloxacin from the priority section of the List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population (Docket No. 98N-0056). For the same reason, FDA is removing trovafloxacin from the priority section of the list.

If you obtain new information that leads you to believe that studying alatrofloxacin or trovafloxacin for an approved indication may generate pediatric information that may produce health benefits in the pediatric population, you may submit a new citizen petition.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Enclosures

99P-1172

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FDA
TALK PAPER

Food and Drug Administration
U.S. Department of Health and Human Services
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FDA ISSUES PUBLIC HEALTH ADVISORY ON LIVER TOXICITY ASSOCIATED WITH THE ANTIBIOTIC TROVAN

The Food and Drug Administration today issued a public health advisory to physicians concerning the risks of liver toxicity associated with the use of Trovan (trovafloxacin, an oral antibiotic) and Trovan-IV (alatrofloxacin, the intravenous formulation of the drug). This action follows postmarketing reports of rare but severe liver injuries leading to transplants and deaths.

In issuing this advisory, FDA is informing physicians that Trovan should be reserved for use only in patients who meet all of the following criteria:

- Patients who have at least one of several specified infections such as nosocomial (hospital-acquired) pneumonia or complicated intra-abdominal infections that, in the judgment of the treating physician, is serious and life- or limb-threatening;
- Patients who begin their therapy in in-patient health care facilities (hospitals or longterm nursing care facilities);
- And patients for whom the treating physician believes that even given the new safety information, the benefit of the product outweighs the potential risks.

FDA is further informing physicians that, in general, therapy with Trovan should not continue for longer than 14 days. Therapy should be discontinued sooner if the patient experiences any clinical signs of liver dysfunction, including fatigue, loss of appetite, yellowing of the skin and eyes, severe stomach pain with nausea and vomiting, or dark urine.

FDA is also advising physicians that for most patients who meet the treatment criteria, therapy would most likely begin with intravenous Trovan. After clinical stabilization patients may be switched to the oral dosage form. Although oral therapy might be appropriate in some cases as an initial therapy, the agency emphasizes that the oral form of Trovan is not warranted for infections other than those specified.

In addition, the manufacturer has agreed to limit distribution of the product to hospitals and long-term nursing care facilities. The manufacturer will be communicating in the near future with other appropriate

pharmacies to provide directions concerning possible return of their present inventories of Trovan.

FDA is taking this action to reduce the potential risk from Trovan, while at the same time preserving for physicians and patients alike the clinical option of an effective broad-spectrum antibiotic for serious and life- threatening infections. The agency considers this advisory an interim measure until revised labeling for the product can be approved.

It is estimated that 2.5 million prescriptions have been written for Trovan, a quinolone antibiotic, since its February 1998 market launch in oral and intravenous formulations. Trovan was initially approved for treating a broad range of infections, from minor skin infections to severe infections in hospitalized patients.

No reports of liver failure, liver transplant, or death due to liver problems were reported in the 7,000 patients studied in premarketing clinical trials for Trovan. In July 1998, FDA worked with the manufacturer to strengthen the product's labeling concerning liver problems after receiving reports of elevated liver enzymes and symptomatic hepatitis in patients after short- and long-term therapy. Since then, FDA has continued to receive reports of liver toxicity, including reports of a more serious nature.

FDA is now aware of 14 cases of acute liver failure that it has concluded are strongly associated with the drug. Six of these patients died: five due to liver failure and one of four additional patients who received liver transplants. Three patients recovered without requiring liver transplants, and for the remaining two patients the final outcome is still pending.

More information about Trovan, including FDA's public health advisory, is available on the World Wide Web at www.fda.gov/cder/news/trovan/default.htm and from Pfizer, the manufacturer of the drug, at 1-800-438-1985.

The FDA asks that any adverse events associated with Trovan be reported to the agency through MedWatch, FDA's adverse event reporting system. Reports may be submitted to FDA by telephone (800-332-1088), by fax (800-332-0178) or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, Md. 20857. Reports can also be filed via the internet at www.fda.gov/medwatch. Reports may also be filed directly to the manufacturer.

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FDA HOME PAGE

Public Health Advisory
Food and Drug Administration

09 June 1999

Trovan
(Trovafloxacin/Alatrofloxacin Mesylate)

INTERIM RECOMMENDATIONS

Trovan (trovafloxacin / alatrofloxacin) was approved by FDA in 1997 for the treatment of a wide variety of infections.

Based on new safety data related to serious liver injury, described below, the Food and Drug Administration is today advising physicians that the drug Trovan should be reserved for use ONLY in the treatment of patients who meet ALL of the following treatment criteria:

- Have at least one of the following infections that is judged by the treating physician to be serious and life- or limb-threatening:
    - nosocomial pneumonia,
    - community acquired pneumonia,
    - complicated intra-abdominal infections (including post-surgical infections)
    - gynecologic and pelvic infections, or
    - complicated skin and skin structure infections, including diabetic foot infections;
- Receive their initial therapy in an in-patient health care facility (i.e., hospital or long-term nursing care facility); and
- The treating physician believes that, even given the new safety information, the benefit of the product for the patient outweighs the potential risk.

In most cases, it is expected that therapy in these patients would begin with the intravenous formulation of Trovan. Due to the bioavailability of oral Trovan, patients who have stabilized clinically on IV therapy may be switched to oral Trovan to complete their course of therapy, if deemed appropriate by the treating physician. In some patients with these kinds of serious and life- or limb-threatening infections, oral Trovan may be considered appropriate initial therapy. Use of oral Trovan to treat less serious infections is not warranted.

Therapy with Trovan beyond 14 days duration generally should not be used, because the risk of liver injury may increase substantially with exposure beyond 14 days. Trovan should be discontinued prior to 14 days of therapy if the patient experiences any clinical signs or symptoms of liver dysfunction, including fatigue, anorexia, yellowing of the skin and eyes, severe stomach pain with nausea and vomiting, or dark urine.

NEW SAFETY DATA

No reports of hepatic failure, liver transplant, or death due to possible hepatic etiology were reported in the 7000 patients in the pre-marketing clinical trials database exposed to Trovan. It is estimated that approximately 2,500,000 patients have received Trovan since approval for marketing. Following marketing of Trovan in the United States in February 1998, FDA began receiving reports of patients who experienced

serious hepatic reactions in association with the use of the product. In July of 1998, FDA had worked with Trovan's manufacturer to add information about hepatic toxicity to the Precautions section of Trovan's package insert.

Since that time, FDA has received reports of over 100 cases of clinically symptomatic liver toxicity in patients receiving Trovan. Some of these patients developed serious liver injury leading to liver transplant and/or death. At present, FDA is aware of 14 cases of acute liver failure that are strongly associated with Trovan exposure. Four of these patients required liver transplant (one of whom subsequently died). Five additional patients died of liver-related illness. Three patients recovered without transplantation, and the final outcome is still pending on two patients. These numbers of patients with acute liver failure, although few, represent a rate that appears to be significantly higher than would be expected to occur idiopathically in the general population - despite the under-reporting of cases that generally occurs to our post-marketing surveillance system.

Trovan-associated liver failure appears to be unpredictable. It has been reported with both short-term (as little as 2 days exposure) and longer-term drug exposure; therefore the efficacy of liver function monitoring in acceptably managing this risk is uncertain.

Trovan use exceeding 2 weeks duration appears to be associated with a substantially increased risk of acute liver failure.

Liver failure has also been reported following Trovan re-exposure.

These uncommon but very serious adverse reactions are typical of drug toxicities which, because of their rarity, may not always be detectable in clinical trials databases. However, such toxicities may become apparent after marketing when the product is used in a significantly broader population. As such, these adverse reactions are the types of important, new safety information the post-marketing spontaneous reporting system is designed to detect, as it did in this case.

CONCLUSIONS

FDA does not wish to deprive patients and physicians of access to effective antimicrobials, if the risks associated with these drugs can be managed successfully by other means. Based on the new safety data presently available to the agency and based on the availability of alternative products to treat other less serious indications for which this product was originally approved, FDA is issuing the interim recommendations outlined above.

FDA and Pfizer have agreed to a program that will limit the distribution of Trovan to in-patient health care facilities (hospitals and long-term nursing care facilities). Pfizer will be communicating in the near future with appropriate pharmacies to provide directions concerning possible return of their present inventories of Trovan.

FDA believes that this risk management program will better ensure that Trovan is used in clinical situations in which its benefits can be expected to outweigh its presently known risks. In this manner, FDA believes that Trovan can continue to be made available to those patients who may need it for treatment of serious and life- or limb-threatening infections, while minimizing other patients' risk of exposure to the product.

FDA advises patients presently taking Trovan NOT to discontinue their therapy until they have discussed their treatment options with their physician.

FDA and the manufacturer will continue to collect and evaluate data on Trovan's safety and will continue to assess the drug's benefit/risk profile. As further information or recommendations about Trovan become available, FDA will continue to inform the health care and patient communities.

FDA requests that any suspected adverse events thought associated with Trovan be reported to the agency through MedWatch, FDA's adverse event reporting system. Reports may be submitted to FDA by telephone (800-332-1088), by fax (800-332-0178) or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, Maryland 20857. Reports can also be filed via the Internet at www.fda.gov/medwatch. Reports may also be filed directly to the manufacturer.

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, Maryland

FDA/Center for Drug Evaluation and Research
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Questions and Answers on Trovafloxacin Public Health Advisory

1. What action is FDA announcing today?

FDA is issuing a Public Health Advisory to inform physicians and the public regarding new safety information about Trovan (trovafloxacin/alatrofloxacin), an antibiotic used to treat many different types of infections. Trovafloxacin was approved for marketing in December, 1997, and became available on the market in February, 1998. Its approved indications include many (14) types of infections that constitute a wide range of degrees of seriousness. Based on new safety data related to serious liver injury, FDA is advising physicians that trovafloxacin should be reserved for treatment ONLY in patients who meet ALL of the following criteria:

- Who have at least one of five types of serious and life or limb-threatening infections listed below that is judged by the treating physician to be serious and life or limb-threatening;
    - Nosocomial pneumonia (pneumonia acquired in the hospital):
    - Community acquired pneumonia
    - Complicated intra-abdominal infections, including post-surgical infections
    - Gynecololgical and pelvic infections
    - Complicated skin and skin structure infections, including diabetic foot infections
- Who begin their therapy in inpatient health care facilities (i.e., hospitals and long term nursing care facilities).
- The treating physician believes that, given the new safety information, the benefit of the product for the patient still outweighs the potential risk.

2. What are the problems occurring with the use of Trovan?

Following the marketing of Trovan in the United States in February 1998, FDA began receiving reports of patients who experienced serious liver reactions in association with use of the product. In July of 1998, FDA worked with the manufacturer to add further information about this toxicity of the drug to Trovan's label, or package insert, in order to inform practitioners . Since that time, FDA has received over 100 reports of cases of patients who were ill with symptoms of liver toxicity, in addition to others in which patients were without symptoms. Some of these patients developed serious liver injury leading to liver transplant and/or death. At present, FDA is aware of 14 cases in patients whose livers actually failed to function that are strongly associated with Trovan exposure.

- Four patients required liver transplantation (one of whom subsequently died).
- Five additional patients died of liver-related disease.
- Three patients recovered from their acute liver failure without requiring a liver transplant.
- The final outcome of two other patients is pending.

Trovan-associated liver failure appears to be unpredictable. It has been reported with treatment duration as short as two days and also in longer term exposure. It has been reported to occur in individuals over a wide range of ages, in men and in women, and in patients who were being treated for a wide variety of types of infection, many of which would not be considered serious or life-threatening. Also, when use exceeds two weeks there appears to be a substantial increase in risk of this toxicity. Liver failure has also been reported following Trovan re-exposure after some period of being off the drug.

These uncommon, but very serious adverse reactions, are typical of drug toxicities which, because of their rarity, may not be detected in clinical trials of drugs before marketing. However, they may become apparent after marketing when wider use of products occur among significantly more people. In the studies of Trovan approximately 7,000 patients were exposed to the drug. No cases of acute liver failure were reported in these pre-market clinical trials.

3. What does "limit distribution" mean?

In this case, the manufacturer of Trovan has agreed to direct distribution of the product only to pharmacies in inpatient health care facilities (i.e., hospitals and long-term nursing care facilities). This, in combination with labeling changes, educational programs and other risk communication strategies, will better ensure that Trovan is only used in clinical situations in which its demonstrated benefits can be expected to outweigh its presently known risks. In this manner, FDA believes that the product can continue to be made available to those patients who need it to treat serious life or limb-threatening infections, while minimizing other patients' risk of exposure to the product.

4. When will the labeling changes take effect?

FDA is working with the manufacturer of Trovan to make appropriate changes to the product's label expeditiously. While the details of that change are being worked out, we are putting forward a Public Health Advisory to inform physicians and patients of this new information.

5. What should patients do if they are currently using Trovan?

Patients should contact their physician. Patients should NOT stop taking Trovan until their physician has recommended that they do so.

6. What are alternative therapies?

Alternative therapies are different depending on what infection the patient is currently being treated for. That is why it is extremely important that patients direct questions about alternative therapy to their physician, who can then make an appropriate recommendation tailored to their needs.

7. How many people are currently using Trovan?

It is estimated that approximately 300,000 prescriptions are written for Trovan per month in the United States.

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